PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number: WO 91/18588
A61K 7/48, 7/075, 7/50 A61K 7/00	A1	(43) International Publication Date: 12 December 1991 (12.12.91)

(21) International Application Number: PCT/FI91/00176

(22) International Filing Date: 5 June 1991 (05.06.91)

(30) Priority data:
533,684 5 June 1990 (05.06.90) US

(71) Applicant: CULTOR LTD. [FI/FI]; P.O. Box 105, Kyllikinportti 2, SF-00241 Helsinki (FI).

(72) Inventor: JUTILA, Kirsti, Maarit ; Rantapolku 2 B 10, SF-02170 Espoo (FI).

(74) Agent: RINKINEN, Raili; Cultor Ltd., P.O. Box 105, Kyllikinportti 2, SF-00241 Helsinki (FI).

(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE, DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB, GB (European patent), GR (European patent), IT (European patent), LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.

(54) Title: A METHOD OF REDUCING THE IRRITATING PROPERTIES OF A COSMETIC COMPOSITION

(57) Abstract

A method for substantially reducing skin irritation and improving moisturizing properties of cosmetics by incorporating a trimethylglycine compound in an effective amount, and cosmetic products produced thereby are disclosed.

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A METHOD OF REDUCING THE IRRITATING PROPERTIES OF A COSMETIC COMPOSITION

BACKGROUND OF THE INVENTION

There is an increasing demand for better and more efficient raw materials for cosmetics and related products. Even the most efficient raw materials can be very irritating or sensitizing for human skin, thus preventing their regular use.

Some of the active compounds in creams, decorative cosmetics, etc., may cause irritation or skin-sensitization. Such active ingredients may include emollients, barrier agents, healing agents, humectants, emulsifiers, preservatives, perfume oils, coloring agents, and/or surfactants, particularly anionic surfactants (e.g., sodium lauryl ether sulphates), and several compounds for skin cleansing (which contain kerosenses, solvents and disinfectants in addition to hard surfactants). Other cosmetics such as deodorants containing ethanol are recognized as having potentially irritating or sensitizing properties. In addition, this problem is often found with many other medicated products.

Cationic compounds such as cetyltrimethylammonium chloride, alkyldimethylbenzylammonium, alkylisoquinidinium, and alkylpyridinium halides are commonly used as hair conditioners. In small amounts, these quaternary ammonium derivatives improve hair manageability.

One drawback of including quaternary ammonium compounds in cosmetics such as shampoos, hair conditioners, creams, lotions, etc. is the fact that great care must be taken when introducing them into commercial products, as most of these materials are known to be skin irritants. More particularly, it is known from the literature that the quaternary compounds of synthetic

origin, particularly at higher concentrations (over 10 percent), cause skin irritation and cauterization.

This problem is overcome in hair conditioners and hair rinses because these preparations are diluted about 15 times with water to form the actual rinse used on the hair. Thus, in general, it has been found that when quaternary compounds are present in concentrations upon dilution with water of 0.1 percent, they are usually still safe and effective on the hair shaft.

Certain other cationic compounds introduced into conditioners have been touted as having a lower level of irritancy than earlier compounds. Examples of such include ethoxylated quaternary ammonium phosphates, quaternized fatty acid amino-amides derived from lanolic acids and mink oil, and N-acyl colaminoformylmethylpyridinium derivatives.

Quaternary ammonium salts have also previously been used at concentrations below 0.1 percent as antiseptics in preparations such as aftershave lotions and baby lotions and creams.

One hair treatment composition, described in U.S. Patent No. 4,752,467 (Konrad et al.), contains 0.1-25 percent by weight betaine and 0.1-10 percent by weight of an aliphatic organic acid such as citric acid. The combination of the betaine/aliphatic organic acid is said to provide synergistic conditioning properties which improve the condition of the hair structure, and act as an antioxidant and as a buffer.

DE-Patent No. 1911144 (Medisan Ab) describes a skin-treating composition for treating abnormal skin conditions or as a vehicle for other medicaments, comprising an aqueous phase in which urea and lactic acid are dissolved. The mode of operation of this composition relates to the skin-softening properties of urea and the keratolytic effect of lactic acid. Optional components

of this composition include emulsifiers and amino acid derivatives such as betaine.

Other cosmetic formulations also include betaine. Betaine is a general name for an organic tertiary amine with three free organic radicals. Known formulations include betaines in which at least one of the free radicals is a long fatty acid derivative based radical. U.S. Patent No. 4,490,355 (Desai) describes a mixture of cocoamidopropyl betaine and oleomidopropyl betaine which when included in cosmetics is said to improve thickening and foam boosting properties. U.S. Patent No. 4,654,161 (Kollmeier et al.) describes the use of organopolysilaxanes that have betaine groups in hair cosmetics. The use of these siloxane derivatives is said to provide improved compatibility with anionic additives (surfactants) and less irritation than prior organopolysiloxanes with quaternary ammonium groups. EP-Patent No. 286261 (Redken Laboratories) describes the use of zwitterions such as taurines and betaines to increase the substantivity of hydrolysed proteins in keratinous tissues.

It is an object of the present invention to provide a method of reducing the skin irritating properties of a cosmetic composition containing substantially no hydrolysed protein.

It is another object of this invention to provide a cosmetic composition which has improved skin compatibility and moisturizing properties.

SUMMARY OF THE INVENTION

It has now been surprisingly discovered that adding an effective amount of a quaternary ammonium like compound which does not have any skin irritating properties to cosmetic compositions reduces the skin irritating properties of skin irritating cosmetics and improves their skin compatibility and moisturizing properties. The present invention also relates to the method of

reducing the skin irritating properties of a cosmetic composition.

The quaternary ammonium compound, preferably obtained from natural sources, is methanaminium, 1-carboxy-N,N,N-trimethyl-,hydroxide inner salt monohydrate or the corresponding anhydride thereof (also referred to as trimethylglycine or trimethylglycine anhydride respectively).

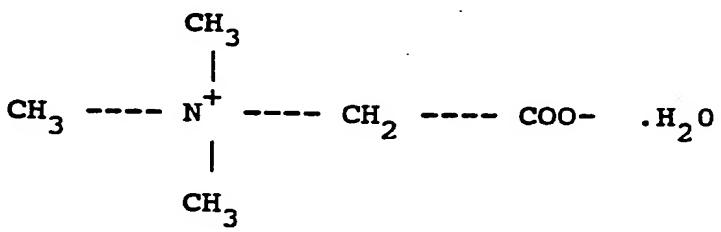
The present invention also relates to a cosmetic composition comprising one or more cosmetic ingredients selected from the group consisting of an active agent, an emollient, a barrier agent, a healing agent, a humectant, an emulsifier, a preservative, a perfume oil, a coloring agent, a deodorizing agent, a surfactant, a solvent and mixtures of the above and one or more of the cosmetic ingredient having irritating properties when applied to human skin, and trimethylglycine or anhydride in an amount effective to substantially neutralize the skin-irritating properties of the cosmetic ingredient.

The dosage of trimethylglycine (or its anhydride) is from about 0.1 to about 50, preferably 1 - 15, percent by weight.

The cosmetic compositions of the present invention include skin cleansers, body shampoos, hair conditioners, skin creams or lotions, deodorants, etc.

DETAILED DESCRIPTION

The addition of trimethylglycine, a natural quaternary ammonium like compound methanaminium, 1-carboxy-N,N,N-trimethyl-,hydroxide inner salt monohydrate or the corresponding anhydride (trimethylglycine/ah)



has now surprisingly been found to reduce the skin irritation properties or sensitisation reactions of cosmetic compounds including irritating ingredients such as sodium lauryl ether sulphate, and other anionic surfactants, cetyltrimethylammonium chloride, alkyl-dimethylbenzylammonium, and alkylisoquinidinium, alkylpyridinium halides, solvents etc. Trimethylglycine (or anhydride thereof) in question has been found to improve the skin compatibility and moisturizing characteristics of cosmetic compositions. Problems mentioned above are often found in products containing irritants, including skin and hand cleaners, skin lotions, skin creams, as well as medicated products. The dosage of methanaminium, 1-carboxy-N,N,N-trimethyl-, hydroxide, inner salt monohydrate or corresponding anhydride is between 0,1 and 50%, preferably 1 - 15 w/w.

The invention is further elucidated by the following examples, which are not meant to limit the claims.

Examples 1-16

The effect of methanaminium, 1-carboxy-N,N,N-trimethyl,-hydroxide, inner salt monohydrate on skin compatibility and irritation were tested by human patch testing.

The patch testing was conducted as follows. In each of these Examples, the test materials were applied on the upper outer arm and the application arm was occluded with a patch for an initial contact period of 24 hours. The patches were then removed and the skin reaction was assessed using a numerical scoring system one hour later.

In order to assess the degree of irritancy, several signs symptomatic of skin irritation and their severity were noted using the scoring system below:

0	=	no visible relevant reaction
1	=	reaction just present
2	=	slight reaction
3	=	moderate reaction
4	=	severe reaction

The signs of irritation were awarded different ratings of significance as follows:

SIGN	ABBREVIATION	RATING
Vesicles	V	5
Odema	Oe	4
Erythema	R	3
Flakiness	F	2
Dryness	D	1
Wrinkling	W	1
Glazing	G	1

In order to obtain a numerical value for the total reaction at each site the severity score for each sign was multiplied by the rating. The resulting values were summed to give a total score for the degree of irritation at that site.

For example, the total score for a site assessed as R3, D2 and G1 would be:

(3 X 3) + (2 X 1) + (1 X 1) = 12

The skin irritation scores for the test and control products were compared statistically using the binomial probability test.

Immediately after assessment an identical fresh patch was applied to the same skin site for a further 24 hours (for a total of 48 hours) and skin reactions were again examined one hour after removal. The materials tested and the mean skin irritation scores after 24 hours and after 48 hours were as follows:

Example	Material Tested	Skin Irritation 24 hr.	48 hr.
1	Deionized water (control)	1.28	0.96
2	Trimethylglycine 50% w/v in deionized water	0.44	0.32
3	sodium lauryl ether sulphate (SLES) 10.3%	1.76	4.28
4	SLES 10.3% + trimethylglycine 7%	0.56	0.80
5	SLES 10.3% + trimethylglycine 5%	0.72	1.92
6	SLES 10.3% + trimethylglycine 3.5%	0.76	2.40
7	SLES 10.3% + trimethylglycine 2%	1.12	2.92
8	SLES 5.15% + trimethylglycine 3.5%	0.88	2.88
9	Deodorant (Control)	0.96	--
10	Deodorant + 5% trimethylglycine	0.65	--
11	Medical cleaner	1.50	2.12
12	Medical cleaner + 5% trimethylglycine	1.27	1.50
13	Eau de cologne	--	--
14	Eau de cologne + 5% trimethylglycine	--	--
15	After Shave Lotion (Control)	1.46	--
16	After Shave Lotion + 5% trimethylglycine	0.85	--

It can be seen from the foregoing numerical results that trimethylglycine significantly reduced the irritancy of the sample to the skin. Where a "--" is indicated in the chart above numerical results were not obtained.

Example 17

Transepidermal Water Loss (TEWL)

Irritants have much stronger effect on dry skin; thus ingredients of cosmetic compounds should not cause any increasing normal TEWL.

The effect of methanaminium, 1-carboxy-N,N,N-trimethyl-,hydroxide inner salt monohydrate on moisturizing and skin smoothness was tested by the transepidermal water loss from skin (TEWL).

In example 17 a leading marketed skin cream was applied under an occlusive patch.

Skin Care Cream (commercially marketed)

Ingredients	
Glycerol monostearate	2.5
Cetyl stearyl ethoxylate	5.0
Emulsifier (Stearic acid)	2.0
White oil	25.0
Glycerol	10.0
Triethanolamine	0.8
Water	Balance

The same cream containing 50% w/w trimethylglycine was applied under an occlusive patch at a different skin site. As a control, blank occlusive patches were also applied to a third skin site. The transepidermal water loss from skin (TEWL) was measured.

The test subjects were twelve female volunteers between 18 and 65 years of age. Panelists were selected on the + criteria that they had normal healthy skin on their forearms and were able to provide stable TEWL values.

Three sites were marked on the volar forearm of each volunteer at approximately equal intervals between the elbow crease and the wrist. The subject was then seated comfortably with her forearms exposed for a period of half an hour so that they would equilibrate with conditions of temperature and relative humidity in the laboratory.

TEWL readings were taken from each skin site to provide normal untreated water loss levels. Treatment was made via 12 mm occlusive Finn chambers. A blank Finn chamber served as the control site. The lotion samples were applied by immersing Whatman 3MM filter paper discs in the sample, removing excess product against the edge

of the container and placing the disc in the Finn chamber using forceps. Each chamber was applied to one of the marked sites on the forearm and held in position with Scanpor non-occulsive surgical tape. The pattern of application of treatments to sites was randomized and recorded.

18 to 24 hours later each subject returned and was re-equilibrated as above. The chambers were then removed and the skin was blotted with tissue to absorb surface moisture. TEWL readings were recorded at 1 minute intervals from the time of removal of treatment until a steady valve was obtained, a period of ten to twenty-five minutes depending on the individual concerned and the treatment applied.

Temperature and relative humidity were recorded at the start of each TEWL reading as gross changes can significantly alter the rate of water loss. The results for each panelist are presented graphically below. An analysis of the results revealed the following:

1) The 1 minute TEWL reading immediately after patch removal is lower for the cream containing trimethylglycine than for the cream alone indicating that the trimethylglycine-treated sites lost water less rapidly. The blank patch control is lower still and represents the skin hydrating effect of occlusion, without adding additional moisture to the skin.

2) The final TEWL value obtained when readings approach a constant value is lower for the cream containing trimethylglycine than for the cream alone, and frequently also the blank control, again indicating better moisture retention at trimethylglycine-treated skin sites.

3) The rate at which the TEWL value decreases towards the normal untreated level is in general more rapid for the cream containing trimethylglycine than for the cream alone or the blank control.

These results are summarized in the table below:

	Initial TEWL level (g/m^2h)			Final TEWL level (g/m^2h)			Time for 75 % reduction in TEWL rate (min)		
Panel No.	Blank	Cream	Cream +TMG	Blank	Cream	Cream +TMG	Blank	Cream	Cream +TMG
1	*	58	40	7	8	5	*	7	5
2	36	50	48	10	12	8	Not reached	14	7
3	34	41	54	8	9	7	16	12	6
4	20	41	*	7	12	8	Not reached	Not reached	*
5	30	63	39	8	18	8	Not reached	Not reached	13
6	17	61	53	9	20	8	Not reached	13	8
7	17	78	45	7	22	3	Not reached	Not reached	5
8	26	71	65	11	26	11	Not reached	Not reached	7
9	25	74	63	6	19	8	11	Not reached	7
10	18	i	34	7	i	6	Not reached	i	7
11	23	53	53	10	17	9	Not reached	Not reached	8
12	26	54	30	6	13	4	17	18	7

The "*" indicates that the evapormeter probe shifted over in the early part of curve so readings were not valid.
The "i" indicates that the patch came loose over the application period.

It can be seen that under these test conditions there were clear indications that the addition of trimethylglycine to the skin cream resulted in improved moisture retention when the product was applied to the skin.

Example 18

Example 18 provides illustrative formulations including ingredient with irritating properties for a skin cream, body shampoo and skin cleanser in accordance with the invention.

Skin cream

Ingredient	Amount (%)
Trioleyl phosphate	3.0
Petrolatum	18.0
Glyceryl stearate	5.0
Isopropyl palmitate	4.0
Cetyl alcohol	2.0
Stearyl heptanoate (irr.)	0.5
Cetearyl octanoate (irr.)	0.5
Sorbitol	5.0
Trimethylglycine	5.0
Water, perfume, preservative (irr.)	q.s.

Shampoo

Ingredient	Amount (%)
Sodium lauryl ether sulphate 30% (irr.)	40.0
Coconut monoethanolamide	2.0
Trimethylglycine	5.0
Perfume, colour, water	q.s.
HCl/NaOH	q.s. to pH 6.5-7.2

Sodium lauryl ether sulphate is known to have a hard cleansing effect; thus because of the side effect (e.g. too effective fat removal from the skin and hair) it

cannot be used as such in shampoos. The addition of trimethylglycine remarkably reduces the irritation effect.

Skin cleanser for oily skin

Ingredient	Amount (%)
Triclosan (deodorising agent; irr.)	3.0
Menthol (irr.)	10.0
DEA-oleth-3 phosphate	2.5
Hydroxypropylcellulose	2.5
Amphoteric-1	5.0
Trimethylglycine	5.0
Water	37.0
Ethanol(96%)	35.0

Trimethyl glycine reduces the irritating properties of irritants.

Example 19 - Smoothness Test

Body Lotion With Improved Skin Compatibility

Ingredient	Amount (%)
Emulsifier	2.0
Cetylalcohol (irr.)	2.5
Isopropylstearate	4.5
Preservative (potential irr.)	0.03
Water	78.77
1,2-Propyleneglycol	6.0
Trimethylglycine	0 or 6.0
Parfum oil	0.2

The effect of methanaminium, 1-carboxy-N,N,N-trimethyl-,hydroxide inner salt monohydrate on skin tested by the Zeiss-spektrophotometer. This formula was tested by using ten female volunteers. The body lotion was used for 8 days. The smoothness of the skin was measured by a Zeiss-spektrophotometer by 660 nm. The results show that the addition of trimethylglycine moderately improves the smoothness of the skin.

Smoothness of skin was calculated by the following equation:

$$= \frac{\text{extinction after treatment}}{\text{initial extinction}} \times 100$$

Results for the ten subjects are reported below:

Age of the volunteer	0%	6% Trimethylglycine
43	99.8	91.8
44	99.3	89.4
51	75.9	59.4
50	98.6	79.3
70	97.5	89.4
47	98.3	91.9
34	100.3	97.1
64	75.4	97.8
30	100.0	97.4
51	95.3	96.5
Average	94.0	89.0

Example 20 - Moisture Holding Capacity Using Corneometer

The same body lotion formula used in Example 19 was used in tests where the moisturizing effect of trimethylglycine was measured by a Corneometer. The moisture holding capacity in the skin was increased when the trimethylglycine level in the product increased from 0% to 2% to 6%.

The same group of test persons and model products were used as in Example 19. Medial part of skin of arms were used (5 x 2.5 cm^2). Different test areas for different model products were used. The instrument used for measurement of the lotions, skin moisturizing effect was a Corneometer Combi (Courage & Khazaka Electronic GmbH, FRG). The subjects were acclimatized in a controlled

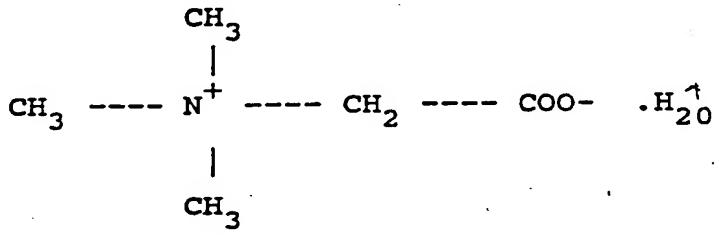
atmosphere (vH 60 %, T° 24°C) for 30 minutes before 0-values of different skin areas were measured. Body lotions were used twice daily (12 hr. intervals). Duration of the trials was 8 days.

The following are hydration measurements made by the Corneometer Combi:

Product	Measurement after Appl.	Minutes 10	20	30	40	60	90	120
Control	107.8	106.3	106.8	107.8	107.7	108.7	107.6	108.2	107.8
0 %	104.5	155.8	118.5	118.4	116.1	115.7	113.2	112.6	111.8
2 %	104.0	152.9	120.0	119.2	115.9	117.1	113.8	113.8	112.8
6 % trimethyl-glycine	103.6	150.4	122.1	118.7	116.1	117.6	116.1	116.3	114.9

PATENT CLAIMS:

1. A method of reducing the skin irritating properties of a cosmetic composition containing substantially no hydrolyzed protein, c h a r a c t e r i z e d by the methanaminium,1-carboxy-N,N,N-trimethyl-, hydroxide, inner salt monohydrate having the chemical structure:

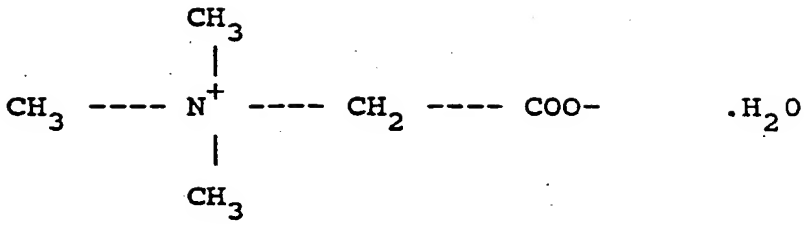


or an anhydride thereof is incorporated into the cosmetic composition in an amount effective to neutralize the skin-irritating properties of the cosmetic composition.

2. The method according to claim 1 c h a r a c t e r i z e d by that the methanaminium,1-carboxy-N,N,N-trimethyl-, hydroxide, inner salt is added in concentration of 0,1 - 50%, preferably 0,1 - 15%, percent by weight.

3. A cosmetic composition having improved skin compatibility and moisturizing properties containing substantially no hydrolysed protein and c h a r a c t e r i z e d by that it comprises a compound having irritating or sensitizing properties when applied to human skin,

an effective amount of a quaternary ammonium like compound, methanaminium,1-carboxy-N,N,N-trimethyl-, hydroxide, inner salt monohydrate having the chemical structure:



or anhydride thereof.

4. The cosmetic composition of claim 3 or 4 characterized by that it is a skin cleanser, a skin cream, or body shampoo.

5. The cosmetic composition of claim 3 or 4 characterized by that the said compound is a deodorant.

The cosmetic composition of claim 3, wherein the concentration of methanaminium, 1-carboxy-N,N,N-trimethyl-, hydroxide, inner salt monohydrate is from 0.1 to 50, preferably from about 0.1 to 15 percent by weight.

The cosmetic composition of claim 3 or 4 characterized by that it is a cream, ointment, emulsion, or an aerosol.

6. A topical preparation according to claim 3 and having improved skin compatibility and moisturizing properties characterized by that it comprises:

(a) one or more cosmetic ingredients selected from the group consisting of an active agent, an emollient, a barrier agent, a healing agent, a humectant, an emulsifier, a preservative, a perfume oil, a coloring agent, a deodorising agent, a surfactant, a solvent and mixtures of the above; and

(b) one or more cosmetic ingredients [may be included in group (a) and] having irritating properties when applied to human skin; and

(c) trimethylglycine or anhydride thereof in an amount effective to neutralize the skin-irritating effects of said cosmetic ingredient.

INTERNATIONAL SEARCH REPORT

International Application No PCT/FI 91/00176

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 K 7/48, 7/075, 7/50, 7/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	WO, A1, 8202337 (WELLA AKTIENGESELLSCHAFT) 22 July 1982, see the whole document --	1-6
X	DE, A1, 3527974 (WELLA AG) 12 February 1987, see the whole document --	1-6
X	DE, A, 1911144 (MEDISAN AB) 17 September 1970, see the whole document --	1-6
X	Patent Abstracts of Japan, Vol 7, No 191, C182, abstract of JP 58- 92607, publ 1983-06-02 --	1-6
X	FR, A, 2303536 (RHONE-POULENC INDUSTRIES) 8 October 1976, see the whole document --	1-6

* Special categories of cited documents:[10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
12th September 1991	1991 -09- 16
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	Elisabeth Carlborg

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/FI 91/00176

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the Swedish Patent Office EDP file on 91-07-31 The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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		CH-A-	594604	78-01-13
		DE-A-	2610225	76-09-23
		GB-A-	1479132	77-07-06
		JP-A-	51113829	76-10-07
		LU-A-	74518	77-01-11
		NL-A-	7602210	76-09-14
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		JP-A-	61171800	86-08-02
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		US-A-	4420410	83-12-13
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